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(54) Title: BIOLOGICALLY DEGRADABLE COMPOSITIONS FOR COATING MEDICAL APPLICATIONS

(57) Abstract: A medical article is disclosed, comprising a biologically degradable AB block copolymer and a biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water.

BIOLOGICALLY DEGRADABLE COMPOSITIONS FOR COATING MEDICAL APPLICATIONS

BACKGROUND

Field of the Invention

5 This invention is relates to biologically degradable compositions for medical applications such as for coatings for implantable medical devices.

Description of the State of the Art

A wide spectrum of devices, from vascular devices such as catheters, stents, and guidewires, to ocular devices such as intra-ocular lenses is incorporating polymeric material.

10 Polymeric materials are being used for a variety of reasons, including making a surface of a device more biocompatible or as a vehicle for delivering a drug. Since polymeric materials are treated as a foreign object by the body's immune system, the challenge has been to make the polymers highly biocompatible as well as to reduce any fouling effects that the polymer may produce or harbor. As a better option, it may be better to make the polymer not only highly

15 biocompatible and non-fouling, but also biodegradable such that the polymer is eliminated by the body after it has served its function. The degradation of the polymer should not create any residues that can provide adverse effects for the patient, such as excess inflammation. To the contrary, the products of degradation should enhance the treatment that is being provided to the patient or should provide medicinal effects. Should the polymeric material include a drug for

20 local application, the composition should be capable of carrying the drug so as to release the drug at an efficacious rate for a therapeutically effective duration of time. Finally, if the material is used as a coating, the properties of the composition should be suitable so as to allow a film layer to be formed on the medical device. For devices that include body geometry that expand or fold,

such as a stent or a balloon, the polymer must be flexible enough so as to expand or fold with the device without significant detachment or delamination of the coating. Tradeoffs do exist between biocompatibility, structural integrity and drug delivery capabilities of the polymer. Enhancing one characteristic may determinately affect the other. Accordingly, a proper balance must be

5 drawn to provide for a polymeric composition that meets the specific need of the application for which it is being used.

The embodiments of the present invention provide for biocompatible polymeric compositions that can be used medical applications.

SUMMARY

10 A medical article is provided comprising a biologically degradable AB block copolymer and a biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water. The medical article can be a stent, a graft or a stent graft. The AB block-copolymer can be capable of absorbing, at equilibrium and at room

15 temperature, about 5 mass % or more water. The AB block-copolymer can include a biocompatible polymeric moiety and a structural polymeric moiety. The biocompatible polymeric moiety can be, for example, poly(alkylene glycol), poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropyl methacrylamide), hydroxylated poly(vinyl pyrrolidone), sulfonated dextran, sulfonated polystyrene, fibrin, fibrinogen, cellulose, starch, collagen, hyaluronic acid, heparin, a graft copolymer of poly(L-lysine)-graft-co-poly(ethylene glycol), and copolymers thereof. The

20 structural polymeric moiety can be poly(D,L-lactide), poly(caprolactone), poly(caprolactone-co-D,L-lactide), poly(butylene terephthalate), poly(ester amide), poly(aspirin), poly(L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), and polydioxanone. The second polymer can be

poly(L-lactide), poly(D,L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(caprolactone), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), poly(ester amides),
5 poly(anhydrides), poly(carbonates), poly(trimethylene carbonate-co-glycolide), poly(trimethylene carbonate-co-L-lactide), poly(trimethylene carbonate-co-D,L-lactide), poly(dioxanone), poly(phosphazenes), poly(orthoesters), poly(tyrosine-co-carbonates), polyalkylene oxalates, poly(glycerol-co-sebacic acid esters), cyanoacrylates, poly(amino acids), poly(lysine), poly(glutamic acid) and combinations thereof.

10 DETAILED DESCRIPTION

Terms and Definitions

For the purposes of the present invention, the following terms and definitions apply:

The terms “biologically degradable” and “biodegradable” are used interchangeably and refer to polymers that are capable of being completely degraded and/or eroded when exposed to
15 bodily fluids such as blood and can be gradually resorbed, absorbed and/or eliminated by the body. The processes of breaking down and eventual absorption and elimination of the polymer can be caused by, for example, hydrolysis, metabolic processes, bulk or surface erosion, and the like. For coating applications, it is understood that after the process of degradation, erosion, absorption, and/or resorption has been completed, no polymer will remain on the device. In some
20 embodiments, very negligible traces or residue may be left behind. Whenever the terms “degradable,” “biodegradable,” or “biologically degradable” are used in this application, they are intended to broadly include biologically erodable, bioabsorbable, and bioresorbable polymers as well as other types of polymers that are broken down and/or eliminated by the body.

units in the copolymers. The term "moiety" as used in the present application is also inclusive of entire polymeric blocks in the copolymers.

Embodiments of the Invention

The biodegradable polymer composition includes at least one biodegradable AB block-copolymer or a polymer that includes biodegradable AB blocks ("the first component") and at least one other biodegradable polymer ("the second component"). The first component can be capable of absorbing, at equilibrium and at room temperature, about 2 mass% or more water, preferably 5 mass% or more water. The second component can be capable of absorbing, at equilibrium and at room temperature, less than about 2 mass % water, preferably less than about 5 mass % water. The second component is not or does not include an AB polymeric block or can include a polymer that is substantially free of AB polymeric blocks. In other words, the second component can include a polymer the molecular structure of which is substantially free of fragments shown by formula (I) above. The ratio between the first component and the second component in the biodegradable polymer composition can be between about 1:1 and about 1:99, more narrowly, between about 1:2 and about 1:49, for example, about 1:19.

THE FIRST COMPONENT (AB BLOCK-COPOLYMER)

The AB block copolymer can be capable of absorbing, at equilibrium and at room temperature, about 2 mass%, preferably about 5 mass % or more water. AB block copolymers that can be used comprise two polymeric moieties A and B. The first polymeric moiety is a biocompatible moiety that can be capable of providing the block-copolymer with blood compatibility. The second polymeric moiety is a structural moiety that can be capable of providing the block-copolymer with mechanical and/or adhesive properties. The structural moiety allows the copolymer to form a film layer on substrates, such as metallic stents. Moiety A can be the biocompatible moiety and moiety B can be the structural moiety. In some

embodiments, Moiety B can be the biocompatible moiety and moiety A can be the structural moiety. The mass ratio between be the biocompatible moiety and the structural moiety can be between about 1:9 and about 1:0.7, for example, about 1:0.81. The mass ratio 1:0.81 corresponds to an AB block-copolymer comprising about 55 mass % the biocompatible moiety and the
5 balance, the structural moiety.

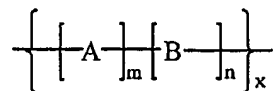
The biocompatible and the structural moieties can be selected to make the AB block-copolymers biologically degradable. Molecular weight of a biocompatible moiety that can be used can be below 40,000 Daltons, for example, between about 300 and 20,000 Daltons. To illustrate, one example of a biocompatible moiety A that can be used is poly(ethylene glycol)
10 (PEG) having the molecular weight between about 300 and 20,000 Daltons. In this example (when the A moiety is PEG), the value of "m" in formula (I) can be between about 5 and about 1,000.

In addition to PEG, other poly(alkylene glycols) can be used to form the biocompatible moiety, for example, poly(propylene glycol) (PPG), poly(tetramethylene glycol), or poly(ethylene
15 oxide-co-propylene oxide). Examples of other biocompatible moieties that can be used include poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropyl methacrylamide), hydroxylated poly(vinyl pyrrolidone), sulfonated dextran, sulfonated polystyrene, fibrin, fibrinogen, cellulose, starch, collagen, hyaluronic acid, heparin, poly(L-lysine)-graft-co-poly(ethylene glycol), which is a graft copolymer of poly(L-lysine) and PEG, or copolymers thereof.

20 Molecular weight of a structural moiety that can be used can be between about 20,000 and about 200,000 Daltons, more narrowly, between about 40,000 and about 100,000 Daltons, for example, about 60,000 Daltons. To illustrate, one example of a structural moiety B that can be used is poly(D,L-lactide) having the molecular weight between about 20,000 and about 200,000

“Biodegradable polymer composition” or “biodegradable composition” is defined as a composition having a combination of at least two biologically degradable polymers. In some embodiments, the composition can also include a non-biologically degradable component or polymer. The polymers can be blended, combined, mixed, bonded, linked by linking agent, or
 5 conjugated.

The term “block-copolymer” is defined in accordance with the terminology used by the International Union for Pure and Applied Chemistry (IUPAC). “Block-copolymer” refers to a copolymer containing a linear arrangement of blocks. The block is defined as a portion of a polymer molecule in which the monomeric units have at least one constitutional or
 10 configurational feature absent from the adjacent portions. The term “AB block-copolymer” is defined as a block-copolymer having moieties A and B arranged according to the general formula



(I)

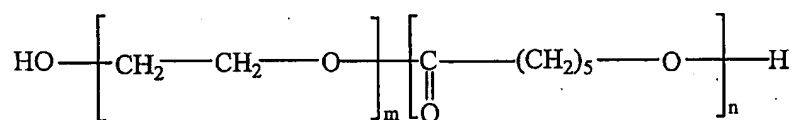
where each of “m,” “n,” and “x” is a positive integer, and m can be ≥ 2 , and n can be ≥ 2 . The
 15 blocks of the AB block-copolymers, could be, but need not be linked on the ends, since the values of the integers “m” and “n” determining the number of blocks are such as to ensure that the individual blocks are usually long enough to be considered polymers in their own right. An AB block copolymer can be, accordingly, named poly A-block-co-poly B block polymer. In some embodiments, the AB block-copolymer can be part of a chain of another polymer such as in the
 20 backbone or as a pendant or side group.

The term “moiety” is defined as a portion of a complete structure of a copolymer, the portion to include at least 2 atoms joined together in a particular way. The term “moiety” includes functional groups and/or discreet bonded residues that are present in the macromolecule of a copolymer. The term “moiety” as used in the present application is inclusive of individual

Daltons. In this example, the value of "n" in formula (I) can be between about 250 and about 3,000.

In addition to poly(D,L-lactide), other structural moieties can be used. Some examples of such moieties include poly(caprolactone) (PCL), poly(caprolactone-co-D,L-lactide),
 5 poly(butylene terephthalate) (PBT), poly(ester amide), poly(aspirin), poly(L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), and polydioxanone.

One example of the biodegradable AB block copolymer is poly(ethylene-glycol)-block-co-
 10 poly(caprolactone) (PEG-PCL). One possible structure of the PEG-PCL block copolymer can be illustrated by formula (II):

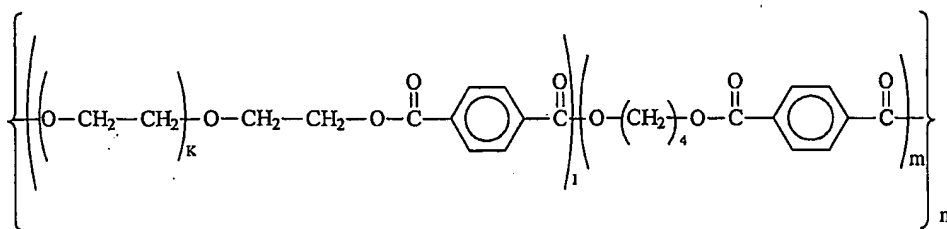


(II)

15 wherein m and n are positive integers.

In PEG-PCL block copolymer shown by formula (II), the PEG blocks constitute the biocompatible moiety A, while the PCL block constitutes the structural moiety B. Block copolymer shown by formula (II) can be synthesized by standard methods known to those having ordinary skill in the art, for example, copolycondensation of PEG with PCL. The process of
 20 copolycondensation can be catalyzed by a catalyst which can be selected by those having ordinary skill in the art, for example, by an acid catalyst or a base catalyst.

Another example of the PEG-containing polyester includes a block-copolymer of PEG with PBT, such as poly(ethylene-glycol)-block-poly(butylene-terephthalate)(PEG-PBT), shown by formula (III):



(III)

wherein m, n, l and K are positive integers.

The PEG-PBT block-copolymer can be obtained by a synthetic process that can be selected by those having ordinary skill in the art. One example of the synthetic process that can be used includes trans-esterification of dibutylene-terephthalate with PEG. One brand of PEG-PBT block copolymer is known under a trade name PolyActive™ and is available from IsoTis Corp. of Holland. In PEG-PBT, the ratio between the PEG units and the PBT units can be between about 0.67:1 and about 9:1. The molecular weight of the PEG units can be between about 300 and about 4,000 Daltons.

PEG-PCL and PEG-PBT block copolymers all contain fragments with ester bonds. Ester bonds are known to be water-labile bonds. When in contact with slightly alkaline blood, ester bonds are subject to catalyzed hydrolysis, thus ensuring biological degradability of the block-copolymer. One product of degradation of every block polymer, belonging to the group PEG-PCL and PEG-PBT, is expected to be PEG, which is highly biologically compatible. PEG also has an additional advantage of being biologically active, reducing smooth muscle cells

proliferation at the lesion site and thus capable of treating, delaying, preventing or inhibiting restenosis.

THE SECOND COMPONENT

The second component of the composition can comprise at least one biodegradable
 5 polymer capable of absorbing, at equilibrium and at room temperature, less than about 2 mass %, preferably less than 5 mass % water.

Examples of suitable biodegradable polymers that can be used as a second component of the biodegradable polymer composition include poly(L-lactide), poly(D,L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(caprolactone),
 10 poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), polyhydroxyalkanoates, poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), poly(ester amides), poly(anhydrides), poly(carbonates), poly(trimethylene carbonate-co-glycolide), poly(trimethylene carbonate-co-L-lactide), poly(trimethylene carbonate-co-D,L-lactide), poly(dioxanone),
 15 poly(phosphazenes), poly(orthoesters), poly(tyrosine-co-carbonates), polyalkylene oxalates, poly(glycerol-co-sebacic acid esters), cyanoacrylates, poly(amino acids), poly(lysine), poly(glutamic acid) and mixtures thereof.

Optional Third Components

In some embodiments, a third component can be included, mixed, blended, bonded,
 20 conjugated or linked with the composition. This can be a drug, an active agent, or a therapeutic substance. In some embodiments, another polymer can be included, mixed, blended, bonded, conjugated or linked with the composition. These polymers need not be biodegradable. Examples include polyacrylates, such as poly(butyl methacrylate), poly(ethyl methacrylate), and poly(ethyl

methacrylate-co-butyl methacrylate), and fluorinated polymers and/or copolymers, such as poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoro propene), poly(vinyl pyrrolidone), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, vinyl halide polymers and copolymers (such as polyvinyl chloride),
5 polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins, e.g., poly(ethylene-co-vinyl alcohol) (EVAL), ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides (such as Nylon 66 and
10 polycaprolactam), alkyd resins, polyoxymethylenes, polyimides, polyethers, epoxy resins, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

The therapeutic substance can include any substance capable of exerting a therapeutic, diagnostic or prophylactic effect for a patient. The therapeutic substance may include small
15 molecule substances, peptides, proteins, oligonucleotides, and the like. The therapeutic substance could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of therapeutic substances include antiproliferative substances such as
20 actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wisconsin, or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant
25 substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g.

- TAXOL[®] by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere[®], from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin[®] from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin[®] from Bristol-Myers Squibb Co., Stamford, Conn.).
- 5 Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc.,
- 10 Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten[®] and Capozide[®] from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil[®] and Prinzide[®] from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine
- 15 antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor[®] from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of
- 20 an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and
- 25 40-O-tetrazole-rapamycin, prodrugs thereof, co-drugs thereof, and combinations thereof.

APPLICATION OF THE COMPOSITION

The composition can have a variety of medical applications, such as coatings for medical devices, coatings for implantable prostheses, capsules for drugs, drug delivery particles as well as devices made at least in part from the composition. Examples of medical devices, that can be used in conjunction with the embodiments of this invention include stents (e.g., self expandable or balloon expandable), biodegradable stents, stent-grafts, grafts (e.g., aortic grafts), catheters, balloons, coating on balloons, guidewires, artificial hearts and valves, blood oxygenators, ventricular assist devices, cardiopulmonary bypass systems, cerebrospinal fluid shunts, pacemaker electrodes, axius coronary shunts and leads as well as other devices such as intraocular lenses. The devices, e.g., the stent, can be made from a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used or coated with the embodiments of the present invention. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

DRUG DELIVERY STENT

A coating for a stent made from the composition of the present invention can be a multi-layer structure and can include a primer layer; a drug-polymer layer (also referred to as "reservoir" or "reservoir layer") or alternatively a polymer free drug layer; and/or a topcoat layer. Intermediary layers can also be provided. Each layer of the stent coating can be formed on the stent by dissolving the biodegradable polymer composition in a solvent, or a mixture of solvents,

and applying the resulting solution on the stent by spraying or immersing the stent in the solution.

At least one of the layers should include the biodegradable polymeric composition of the present invention. The remaining portion of a layer or the other layers can be made from other polymeric material, such as poly(butyl methacrylate), poly(ethyl methacrylate), and poly(ethyl methacrylate-co-butyl methacrylate), or the others disclosed above.

Preferably, the outer most layer (e.g., the reservoir layer or the topcoat layer) is made from the biodegradable composition. If a topcoat layer is used, the topcoat layer can be made from the biodegradable polymer. The reservoir layer or the optional primer layer can be made from the same composition, the same composition but with different ratios of the first to second component, the same composition but with different ratios of the first to second to third component or from a different polymeric material.

In some embodiments at least two of the layers can be made from the embodiments of the biodegradable polymeric composition such that for each layer the ratio of the first to second component is different. In some embodiments, if a third component is used, the ratio of the first to second to third component can be different for each layer.

After the solution has been applied onto the stent, the coating is dried by allowing the solvent to evaporate. The process of drying can be accelerated if the drying is conducted at an elevated temperature.

Representative examples of some solvents suitable for making the coating solution include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), cyclohexanone, xylene, toluene, acetone, *i*-propanol, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, *n*-butyl acetate, and dioxane. Some solvent mixtures can be used as well. Representative examples of the mixtures include DMAC and methanol (e.g., a 50:50 by mass mixture); water, *i*-propanol, and DMAC (e.g., a 10:3:87 by

- mass mixture); *i*-propanol and DMAC (e.g., 80:20, 50:50, or 20:80 by mass mixtures); acetone and cyclohexanone (e.g., 80:20, 50:50, or 20:80 by mass mixtures); acetone and xylene (e.g. a 50:50 by mass mixture); acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture); and 1,1,2-trichloroethane and chloroform (e.g., a 80:20 by mass mixture). FLUX
- 5 REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance of methanol, with trace amounts of nitromethane. Those having ordinary skill in the art will select the solvent or a mixture of solvents suitable for a particular polymer being dissolved.
- 10 To incorporate a drug into the reservoir layer, the drug in a form of a solution can be combined with the polymer solution that is applied onto the stent as described above. Alternatively, to fabricate a polymer free drug layer, the drug can be dissolved in a suitable solvent or mixture of solvents, and the resulting drug solution can be applied on the stent by spraying or immersing the stent in the drug solution. Instead of introducing the drug in a solution,
- 15 the drug can be introduced as a colloid system, such as a suspension in an appropriate solvent phase. To make the suspension, the drug can be dispersed in the solvent phase using conventional techniques used in colloid or emulsion chemistry. Depending on a variety of factors, e.g., the nature of the drug, those having ordinary skill in the art can select the suitable solvent to form the solvent phase of the suspension, as well as the quantity of the drug to be dispersed in the solvent
- 20 phase. The suspension can be mixed with a polymer solution and the mixture can be applied on the stent as described above. Alternatively, the drug suspension can be applied on the stent without being mixed with the polymer solution.

The biological degradation of the biodegradable polymer composition is expected to cause an increase of the rate of release of the drug due to the gradual disappearance of the polymer that

25 forms the reservoir and/or the topcoat layer. By choosing an appropriate biodegradable polymer

composition or by varying the ratio of the components of the composition, or by including a third polymeric component to the matrix, a stent coating having a costumed release rate can be engineered.

Method of Use

5 In accordance with embodiments of the invention, a coating of the various described embodiments can be formed on an implantable device or prosthesis, e.g., a stent. For coatings including one or more active agents, the agent will be retain on the medical device such as a stent during delivery and expansion of the device, and released at a desired rate and for a predetermined duration of time at the site of implantation. Preferably, the medical device is a stent. A stent
10 having the above-described coating is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating is particularly useful for treating occluded regions of blood vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis.
15 Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries.

The compositions of the invention can be used for the treatment of a variety of disorder in mammals including atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication,
20 anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, cancer as well as other disorders.

For implantation of a stent, an angiogram is first performed to determine the appropriate positioning for stent therapy. An angiogram is typically accomplished by injecting a radiopaque contrasting agent through a catheter inserted into an artery or vein as an x-ray is taken. A
25 guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire

is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above-described coating may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

Examples

The following examples are provided to further illustrate embodiments of the present invention.

Example 1

A first composition can be prepared by mixing about 1.0 mass % to about 15 mass %, for example, about 2.0 mass % poly(caprolactone) (PCL); and the balance, mixture of tetrahydrofuran (THF) and xylene solvents, where a mass ratio between THF and xylene was about 3:1. The first composition can be applied onto the surface of a bare 12 mm VISION stent (available from Guidant Corporation) by spraying and dried to form a primer layer. A spray coater was used, having a 0.014 fan nozzle maintained at about 60° C with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). About 75 µg of the wet coating can be applied. The primer was baked at about 60° C for about 2 hours, yielding a dry primer layer.

A second composition can be prepared by mixing about 1.0 mass % to about 15 mass %, for example, about 2.0 mass % PCL; about 0.05 mass % to about 2.0 mass %, for example, about 1.0 mass % EVEROLIMUS; and the balance, THF/xylene solvent mixture described above. The second composition can contain about 300 µg PCL and about 150 µg EVEROLIMUS. The second composition can be applied onto the dried primer layer to form the reservoir layer, using

the same spraying technique and equipment used for applying the primer layer, followed by drying, e.g., by baking at about 50° C for about 1 hour. A third composition can be prepared by mixing about 1.0 mass % to about 15 mass %, for example, about 2.0 mass % PCL; about 1.0 mass % to about 15 mass %, for example, about 2.0 mass % PEG-PBT (4000PEGT80PBT20);
5 and the balance, THF/xylene solvent mixture described above.

The brand of PEG-PBT that can be used can have about 20 molar % PBT units and about 80 molar % PEG units. The molecular weight of the PEG units was about 4,000 Daltons. The third composition can contain about 50 µg PCL and about 50 µg PEG-PBT. The third composition can be applied onto the dried reservoir layer to form a topcoat layer, using the same
10 spraying technique and equipment used for applying the primer layer and the reservoir layer, followed by drying at about 50°C for about 1 hour.

Example 2

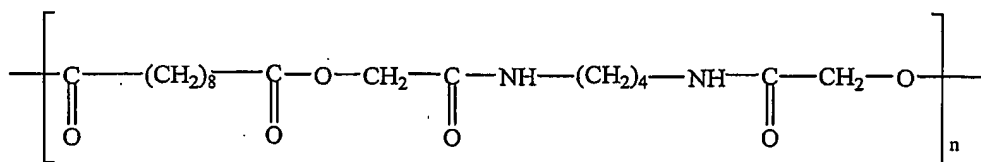
A primer and reservoir layers can be formed on a stent as described in Example 1. A composition can be prepared by mixing about 1.0 mass % to about 15 mass %, for example, about
15 2.0 mass % poly(L-lactide); about 1.0 mass % to about 15 mass %, for example, about 2.0 mass % PEG-PBT; and the balance, the mixture of chloroform and trichloroethane solvents, wherein the mass ratio between chloroform and trichloroethane can be about 1:1. The same brand of PEG-PBT as described in Example 1 can be used. The composition can contain about 60 µg poly(L-lactide), about 40 µg PEG-PBT, and if desired, about 200 µg paclitaxel. The composition can be applied
20 onto the dried reservoir layer to form a topcoat layer.

Example 3

A primer and reservoir layers can be formed on a stent as described in Example 1, except rapamycin can be used instead of EVEROLIMUS. A composition can be prepared by mixing

about 1.0 mass % to about 15 mass %, for example, about 1.5 mass % poly(ester amide); about 1.0 mass % to about 15 mass %, for example, about 0.5 mass % PEG-PBT; and the balance, a mixture of ethanol and DMAC solvents, wherein mass ratio between ethanol and DMAC can be about 1:1.

- 5 The same brand of PEG-PBT as described in Example 1 can be used. Poly(ester amide)-8,4 having the formula (IV) can be used:



(IV)

wherein n is a positive integer.

- 10 The composition can contain about 75 µg poly(ester amide), and about 25 µg PEG-PBT. The composition can be applied onto the dried reservoir layer to form a topcoat layer, using the same spraying technique and equipment as described above, followed by drying, e.g., by baking. The poly(ester amide) shown by formula (IV) is expected to degrade when exposed to bodily fluids such as blood to yield sebacic and glycolic acids and 1,4-butanediamine (putrescine), all of which are biocompatible.
- 15

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

20

CLAIMS

WHAT IS CLAIMED IS:

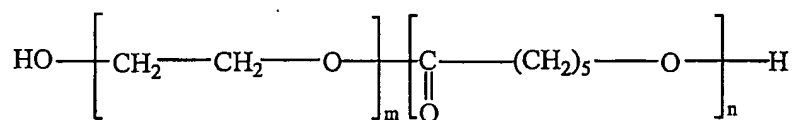
1. A medical article, comprising:
 - (a) a medical substrate; and
 - 5 (b) a coating deposited on the substrate, the coating comprising a first polymer and a second polymer, wherein the first polymer includes a biologically degradable AB block copolymer, and the second polymer includes a biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water.
- 10 2. The medical article of Claim 1, wherein the medical article is a stent, graft, or a stent-graft.
3. The medical article of Claim 1, wherein the AB block-copolymer is capable of absorbing, at equilibrium and at room temperature, about 5 mass % or more water.
4. The medical article of Claim 1, wherein the second polymer does not include or is substantially free from AB polymeric blocks.
- 15 5. The medical article of Claim 1, wherein the AB block-copolymer comprises a biocompatible polymeric moiety and a structural polymeric moiety.
6. The medical article of Claim 5, wherein the biocompatible polymeric moiety is selected from a group consisting of a poly(alkylene glycol), poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropyl methacrylamide), hydroxylated poly(vinyl pyrrolidone), sulfonated
20 dextran, sulfonated polystyrene, fibrin, fibrinogen, cellulose, starch, collagen, hyaluronic acid, heparin, a graft copolymer of poly(L-lysine)-graft-co-poly(ethylene glycol), and copolymers thereof.

7. The medical article of Claim 6, wherein the poly(alkylene glycol) is selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), and poly(ethylene oxide-co-propylene oxide).

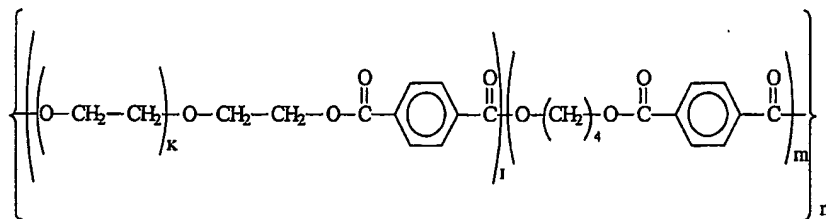
8. The medical article of Claim 5, wherein the structural polymeric moiety is selected from a group consisting of poly(D,L-lactide), poly(caprolactone), poly(caprolactone-co-D,L-lactide), poly(butylene terephthalate), poly(ester amide), poly(aspirin), poly(L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), and polydioxanone.

9. The medical article of Claim 1, wherein the AB block-copolymer is selected from poly(ethylene-glycol)-block-co-poly(caprolactone) and poly(ethylene-glycol)-block-co-poly(butylene terephthalate).

10. The medical article of Claim 1, wherein the AB block-copolymer is:



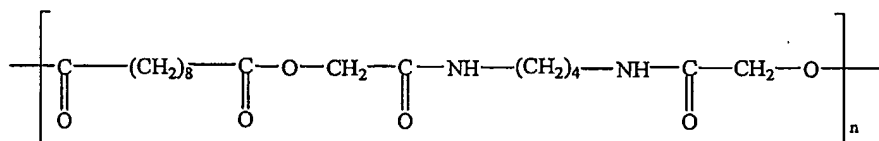
15 or



wherein m, n, I, K, and r are positive integers.

11. The medical article of Claim 1, wherein the second polymer is selected from a group consisting of poly(L-lactide), poly(D,L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(caprolactone), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), polyhydroxyalkanoates, poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), poly(ester amides), poly(anhydrides), poly(carbonates), poly(trimethylene carbonate-co-glycolide), poly(trimethylene carbonate-co-L-lactide), poly(trimethylene carbonate-co-D,L-lactide), poly(dioxanone), poly(phosphazenes), poly(orthoesters), poly(tyrosine-co-carbonates), polyalkylene oxalates, poly(glycerol-co-sebacic acid esters), cyanoacrylates, poly(amino acids), poly(lysine), poly(glutamic acid) and combinations thereof.

12. The medical article of Claim 1, wherein the second polymer has the formula:



wherein n is a positive integer.

13. The medical article of Claim 1, additionally including a therapeutic substance,

14. A medical article, comprising a biologically degradable AB block copolymer and a biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water.

15. The article of Claim 14, wherein the medical article is a stent, a graft or a stent graft.

16. The article of Claim 14, wherein the AB block-copolymer is capable of absorbing, at equilibrium at room temperature, about 5 mass % or more water.

17. The article of Claim 14, wherein the second polymer does not include or is substantially free from AB polymeric blocks.

5 18. The article of Claim 14, wherein the AB block-copolymer comprises a biocompatible polymeric moiety and a structural polymeric moiety.

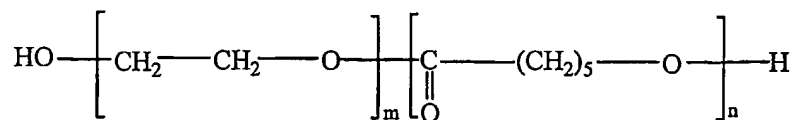
19. The article of Claim 18, wherein the biocompatible polymeric moiety is selected from a group consisting of a poly(alkylene glycol), poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropyl methacrylamide), hydroxylated poly(vinyl pyrrolidone), sulfonated dextran,
10 sulfonated polystyrene, fibrin, fibrinogen, cellulose, starch, collagen, hyaluronic acid, heparin, a graft copolymer of poly(L-lysine)-graft-co-poly(ethylene glycol), and copolymers thereof.

20. The article of Claim 19, wherein the poly(alkylene glycol) is selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), and poly(ethylene oxide-co-propylene oxide).

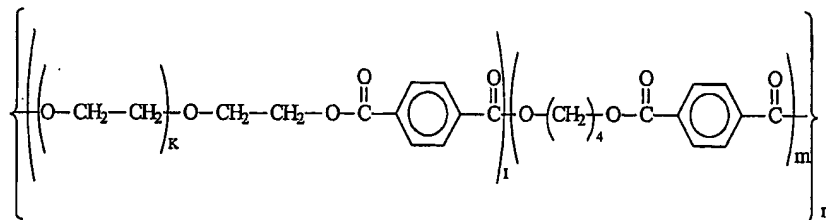
15 21. The article of Claim 18, wherein the structural polymeric moiety is selected from a group consisting of poly(D,L-lactide), poly(caprolactone), poly(caprolactone-co-D,L-lactide), poly(butylene terephthalate), poly(ester amide), poly(aspirin), poly(L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-
20 hydroxybutyrate-co-valerate), and polydioxanone.

22. The article of Claim 14, wherein the AB block-copolymer is selected from poly(ethylene-glycol)-block-co-poly(caprolactone) and poly(ethylene-glycol)-block-co-poly(butylene terephthalate).

23. The article of Claim 14, wherein the AB block-copolymer is



or



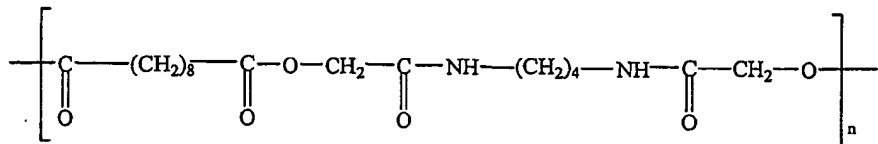
5 wherein m, n, I, K, and r are positive integers.

24. The article of Claim 14, wherein the biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water is selected from a group consisting of poly(L-lactide), poly(D,L-lactide), poly(glycolide), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(caprolactone), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), polyhydroxyalkanoates, poly(3-hydroxybutyrate), poly(4-hydroxybutyrate), poly(hydroxyvalerate), poly(3-hydroxybutyrate-co-valerate), poly(4-hydroxybutyrate-co-valerate), poly(ester amides), poly(anhydrides), poly(carbonates), poly(trimethylene carbonate-co-glycolide), poly(trimethylene carbonate-co-L-lactide), poly(trimethylene carbonate-co-D,L-lactide), poly(dioxanone), poly(phosphazenes), poly(orthoesters), poly(tyrosine-co-carbonates), polyalkylene oxalates, poly(glycerol-co-sebacic acid esters), cyanoacrylates, poly(amino acids), poly(lysine), poly(glutamic acid) and combinations thereof.

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25. The article of Claim 14, wherein the biologically degradable polymer that is capable, at equilibrium and at room temperature, of absorbing less than about 5 mass % water is:



wherein n is a positive integer.

26. The article of Claim 14, additionally including a therapeutic agent mixed, bonded, conjugated, linked or blended with the block copolymer and/or the polymer.

5 27. A method of treating a disorder in a human being, comprising:

implanting in the human being a medical article as defined in claim 14, wherein the disorder is selected from the group consisting of atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein and artificial grafts, bile duct

10 obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/34 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/090807 A (POLY-MED, INC; SHALABY, SHALABY, W) 6 November 2003 (2003-11-06) page 2, line 24 - page 3, line 24 claims 1,17,18	1-27
E	WO 2005/051449 A (ADVANCED CARDIOVASCULAR SYSTEMS, INC; HOSSAINY, SYED, F.A; TANG, YIWEN) 9 June 2005 (2005-06-09) claims 1,2,5,7,8,16-18	1-27
A	US 2003/162905 A1 (BENZ MICHAEL ERIC ET AL) 28 August 2003 (2003-08-28) page 2, left-hand column, paragraph 18 - right-hand column, paragraph 22	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

16 September 2005

Date of mailing of the international search report

23/09/2005

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009881

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/009881

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 03090807	A	06-11-2003	AU	2003239175 A1	10-11-2003
			EP	1499367 A1	26-01-2005
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			EP	1482997 A1	08-12-2004
			JP	2005518841 T	30-06-2005
			WO	03072158 A1	04-09-2003
			US	2004214955 A1	28-10-2004